

ORIGINAL ARTICLE – BREAST ONCOLOGY

Present-Day Locoregional Control in Patients with T1 or T2 Breast Cancer with 0 and 1 to 3 Positive Lymph Nodes After Mastectomy Without Radiotherapy

Ranjna Sharma, MD¹, Isabelle Bedrosian, MD¹, Anthony Lucci, MD¹, Rosa F. Hwang, MD¹, Loren L. Rourke, MD¹, Wei Qiao, MS², Thomas A. Buchholz, MD³, Steven J. Kronowitz, MD⁴, Savitri Krishnamurthy, MD⁵, Gildy V. Babiera, MD¹, Ana M. Gonzalez-Angulo, MD⁶, Funda Meric-Bernstam, MD¹, Elizabeth A. Mittendorf, MD¹, Kelly K. Hunt, MD¹, and Henry M. Kuerer, MD, PhD, FACS¹

¹Department of Surgical Oncology, Unit 444, The University of Texas M. D. Anderson Cancer Center, Houston, TX;

²Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston, TX; ³Department of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX; ⁴Department of Plastic Surgery, The University of Texas M. D. Anderson Cancer Center, Houston, TX; ⁵Department of Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, TX; ⁶Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX

ABSTRACT

Background. We sought to determine present-day locoregional recurrence (LRR) rates to better understand the role of postmastectomy radiotherapy (PMRT) in women with 0 to 3 positive lymph nodes.

Methods. Clinical and pathologic factors were identified for 1019 patients with pT1 or pT2 tumors and 0 (*n* = 753), 1 (*n* = 176), 2 (*n* = 69), or 3 (*n* = 21) positive lymph nodes treated with mastectomy without PMRT during 1997 to 2002. Total LRR rates were calculated by Kaplan-Meier analysis and compared between subgroups by the log rank test.

Results. After a median follow-up of 7.47 years, the overall 10-year LRR rate was 2.7%. The only independent predictor of LRR was younger age (*P* = 0.004). Patients ≤40 years old had a 10-year LRR rate of 11.3 vs. 1.5% for older patients (*P* < 0.0001). The 10-year rate of LRR in patients with 1 to 3 positive nodes was 4.3% (94.4% had systemic therapy), which was not significantly different

from the 10-year risk of contralateral breast cancer development (6.5%; *P* > 0.5). Compared with the 10-year LRR rate among patients with node-negative disease (2.1%), patients with 1 positive node had a similar 10-year LRR risk (3.3%; *P* > 0.5), and patients with 2 positive nodes had a 10-year LRR risk of 7.9% (*P* = 0.0003). Patients with T2 tumors with 1 to 3 positive nodes had a 10-year LRR rate of 9.7%.

Conclusions. In patients with T1 and T2 breast cancer with 0 to 3 positive nodes, LRR rates after mastectomy are low, with the exception of patients ≤40 years old. The indications for PMRT in patients treated in the current era should be reexamined.

The importance of locoregional control in breast cancer cannot be overestimated. More than a decade has passed since the landmark publication of two randomized trials demonstrating a survival advantage from the addition of postmastectomy radiotherapy (PMRT) in patients at high risk for locoregional recurrence (LRR) after mastectomy.^{1,2} The addition of radiotherapy after definitive mastectomy can decrease the risk of LRR by 75%.³

Until the 2005 publication of the Oxford overview showing that one breast cancer-specific death can be prevented for every four LRRs avoided, the use of PMRT in women with node-negative breast cancer or 1 to 3 positive lymph nodes was generally considered somewhat controversial, except in patients perceived to be at highest risk for

Presented in part at the Society of Surgical Oncology 63rd Annual Cancer Symposium Plenary Session, St. Louis, MO, March 6, 2010.

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First Received: 4 February 2010;
Published Online: 5 May 2010

H. M. Kuerer, MD, PhD, FACS
e-mail: hkuerer@mdanderson.org

LRR.^{4–6} During a 2007 American Society of Clinical Oncology session, the Early Breast Cancer Trialists' Collaborative Group presented updated preliminary subgroup analyses of patients with 1 to 3 positive nodes treated on randomized trials of PMRT (commencing during 1964 to 1984) that showed statistically improved 15-year breast cancer mortality rates among patients receiving radiotherapy.⁷ On the basis of the Oxford overview and other published survival data and previous reports of LRR rates ranging from 11 to 33% in patients with 1 to 3 positive nodes treated without radiotherapy, there has been a marked increase in the use of PMRT in patients with 1 to 3 positive lymph nodes.^{4,6,8–13} Since 2007, the National Comprehensive Cancer Network Breast Cancer Practice Guidelines have also strongly recommended consideration of PMRT in patients with 1 to 3 positive lymph nodes.¹⁴ In many centers, the current practice of using PMRT in patients with 1 to 3 positive nodes has resulted in patients' being denied immediate breast reconstruction because PMRT after immediate reconstruction is associated with severe tissue effects, unacceptably high rates of complications, and poor cosmetic outcome.^{15–17}

The previously reported rates of LRR after mastectomy without postoperative radiotherapy do not reflect recent advances in early detection, surgery, and systemic treatment. We hypothesized that rates of LRR after mastectomy without PMRT in patients with 1 to 3 positive lymph nodes are much lower among patients treated within the past decade than among patients treated in earlier series. To test this hypothesis, we performed a retrospective review of patients treated at our comprehensive cancer center during 1997–2002.

METHODS

After we obtained institutional review board approval for this study, 1019 patients were identified from the prospectively maintained M. D. Anderson Cancer Center Breast Cancer Management Database who met the following eligibility and exclusion criteria: diagnosis between 1997 and 2002; stage I or II breast cancer (pT1 or pT2 invasive breast cancer without lymph node involvement or with 1 to 3 positive lymph nodes on final pathologic analysis); mastectomy with negative margins for both invasive or noninvasive disease; either axillary lymph node dissection or intraoperative lymphatic mapping and sentinel node biopsy; no neoadjuvant systemic therapy; and no PMRT. For patients with bilateral breast cancer at diagnosis ($n = 50$), pathologic information from the side with the highest tumor and nodal stage was used for subsequent analyses.

LRR was defined as recurrence in the ipsilateral chest wall or axillary, supraclavicular, infraclavicular, or internal

mammary lymph nodes. LRR rates included all LRRs with or without previous or simultaneous distant metastasis. Disease at any other site was considered distant metastasis. Actuarial rates of total LRR, disease-free survival (DFS), and development of contralateral breast cancer were calculated by the Kaplan-Meier method, and clinical and pathologic comparisons among groups were calculated by the log rank test. The date of last follow-up was defined as the date of the last clinic visit at M. D. Anderson Cancer Center, the date of last clinical correspondence or death. The Cox proportional hazard regression model was used for multivariate analyses, and all P values of <0.05 were considered significant.

RESULTS

Patient, pathologic, and treatment characteristics for the 1019 patients are listed in Table 1. The median age for all patients was 54 years (range, 25–91 years). Median follow-up time was 7.47 years (range, 0.23–11.7 years; 95% confidence interval [95% CI], 7.23–7.52). Most patients (78.8%) had T1 tumors.

The method of initial nodal staging was axillary lymph node dissection in 694 patients and lymphatic mapping and sentinel lymph node biopsy in 325 patients. Two hundred sixty-six patients (26.2%) had positive lymph nodes; of these patients, 189 (70.8%) had T1 disease. The size of the largest nodal metastasis was ≤ 1 cm in 75.6% of patients. The median number of lymph nodes removed in patients who had axillary dissection was 16 (95% CI, 15.6–16.6).

Although most patients (76.9%) received adjuvant chemotherapy or hormonal therapy, patients with node-positive disease were significantly more likely than those with node-negative disease to receive adjuvant systemic therapy (94.4 vs. 70.9%; $P < 0.000001$).

Locoregional Recurrence

Twenty-three patients (2.3%) had LRR (Table 2). The median time to LRR was 3.84 years (95% CI, 3.26–3.84). Of the 23 patients with a LRR, 14 had T1 tumors and 9 had T2 tumors; 10 had stage I, 7 had stage IIA, and 6 had stage IIB disease. Location of the LRR was the chest wall in 11 patients (47.8%); supraclavicular lymph nodes in 7 patients (30.4%); internal mammary chain in 2 patients (8.7%); and multiple locations affected synchronously in 3 patients (13.0%); chest wall and internal mammary chain, supraclavicular region and internal mammary chain, and axillary nodal basin and supraclavicular region). LRR was the only recurrence event in 11 patients (47.8%). The other 12 patients with LRR had LRR diagnosed concurrently with distant metastasis (7 patients; 30.4%), before distant

TABLE 1 Patient, pathologic, and treatment characteristics among 1019 patients treated with mastectomy without radiotherapy

Characteristic	n (%)
Age (years)	
≤40	113 (11.1)
41–50	273 (26.8)
51–60	291 (28.6)
61–70	204 (20)
>70	138 (13.5)
Race and/or ethnicity	
Non-Hispanic white	809 (79.3)
Hispanic white	94 (9.2)
Black	68 (6.7)
Asian/Pacific Islander	35 (3.4)
Other	14 (1.4)
Tumor classification	
T1a	173 (17)
T1b	186 (18.3)
T1c	444 (43.5)
T2	216 (21.2)
Nodal status	
N0	753 (73.8)
N1	266 (26.2)
No. of positive nodes	
0	753 (73.8)
1	176 (17.3)
2	69 (6.8)
3	21 (2.1)
Nodal metastases, largest recorded size	
≤1 cm	202 (75.6)
>1 cm	41 (15.4)
Not recorded	23 (9.0)
Extranodal extension	
None	225 (84.6)
<2 mm	30 (11.3)
≥2 mm	11 (4.1)
Stage	
I	613 (60.1)
IIA	329 (32.4)
IIB (T2N1)	77 (7.5)
Estrogen receptor status	
Negative	212 (22.3)
Positive	733 (77.1)
Not tested	74 (7.3)
HER2 status	
Negative	467 (45.8)
Positive	189 (18.5)
Not tested	363 (35.7)

TABLE 1 continued

Characteristic	n (%)
Lymphovascular invasion	
None	883 (86.7)
Present	136 (13.3)
Grade	
I	56 (5.5)
II	494 (48.4)
III	453 (44.5)
Not recorded	16 (1.6)
Adjuvant chemotherapy regimen	
None	595 (58.4)
Doxorubicin based	241 (23.6)
Doxorubicin and taxane based	161 (15.8)
Other	22 (2.2)
Adjuvant hormone therapy	
None	380 (37.4)
Received	639 (62.6)
Any adjuvant therapy	
None	234 (23.1)
Received	784 (76.9)
Immediate reconstruction	
None	524 (51.3)
Received	495 (48.6)

metastasis (3 patients; 13%), or after distant metastasis (2 patients; 8.7%). Seventy percent of patients ($n = 16$) with a LRR underwent immediate breast reconstruction (six were bilateral). Eighteen patients (78.3%) with an LRR received adjuvant systemic therapy.

Clinical and Pathologic Factors Associated with LRR

Table 2 details the 5- and 10-year rates of LRR with respect to patient, pathologic, and treatment characteristics. On univariate analyses, younger age, T2 tumors, positive lymph nodes, higher stage, estrogen receptor status, and receipt of adjuvant chemotherapy were associated with increased risk of LRR (Table 2). Patients who received adjuvant chemotherapy were significantly more likely to have T2 tumors (T2 = 60.2%, T1 = 36.6%; $P < 0.000001$), have node-positive disease (node positive = 73%, node negative = 29.6%; $P < 0.00001$), and be younger (≤ 40 years = 69.9%, > 40 years = 38%; $P < 0.00001$). Patients who received endocrine therapy were significantly less likely to have LRR (Table 2).

TABLE 2 Five- and 10-year locoregional recurrence (LRR) rates with regard to patient, pathologic, and treatment-related factors

Factor	No LRR, n (%)	LRR, n (%)	5-year LRR rate (%)	10-year LRR rate (%)	P value
Overall	997 (97.7)	23 (2.3)	1.6	2.7	—
Age (years)					
≤40	102 (10.2)	11 (47.8)	5.5	11.3	
41–50	266 (26.7)	7 (30.4)	1.5	3.0	
51–60	288 (29.0)	3 (13.0)	1.1	1.1	
61–70	203 (20.4)	1 (4.3)	0.6	0.6	
>70	137 (13.7)	1 (4.3)	0.9	0.9	<0.0001
Tumor classification					
T1	790 (79.2)	14 (60.9)	1.0	2.1	
T2	206 (20.8)	9 (39.1)	3.7	5.1	0.02
No. of positive nodes					
0	739 (74.3)	13 (56.5)	1.1	2.1	
1	171 (17.2)	5 (21.7)	2.5	3.3	
2	64 (6.4)	5 (21.7)	4.5	7.9	
3	21 (2.1)	0 (0)	0.0	0	0.02
Nodal status					
N0	739 (74.3)	13 (56.5)	1.1	2.1	
N1	256 (25.7)	10 (43.5)	2.9	4.3	0.05
Nodal metastases, largest recorded size ^a					
≤1 cm	195 (83.3)	7 (77.8)	3.2	4.0	
>1 cm	39 (16.7)	2 (22.2)	2.9	6.4	0.74
Positive nodes, 0 vs. 1					
0	739 (81.2)	13 (72.2)	1.1	2.1	
1	171 (18.8)	5 (27.8)	2.5	3.3	0.3
Positive nodes, 0 vs. 2					
0	739 (92.0)	13 (72.2)	1.1	2.1	
2	64 (8.0)	5 (27.8)	4.5	7.9	0.003
Extranodal extension					
None	204 (83.9)	21 (91.3)	1.5	2.6	
<2 mm	29 (11.9)	1 (4.3)	0.0	3.6	
≥2 mm	10 (4.1)	1 (4.3)	10.0	10	0.33
Stage					
I	603 (60.5)	10 (43.5)	0.8	2.0	
IIA	322 (32.4)	7 (30.4)	2.0	2.4	
IIB (T2, N1)	71 (7.1)	6 (26.1)	5.8	9.7	0.001
Estrogen receptor status ^b					
Negative	204 (22)	8 (40)	2.6	5.0	
Positive	721 (78)	12 (60)	1.2	1.9	0.03
HER2 status ^c					
Negative	461 (71.6)	6 (50)	0.9	1.5	
Positive	183 (28.4)	6 (50)	2.3	4.1	0.1
Lymphovascular invasion					
None	863 (86.7)	20 (87)	1.7	2.7	
Present	133 (13.3)	3 (13)	0.8	2.8	0.996
Grade ^d					
1	56 (5.7)	0 (0)	0.0	0.0	
2	486 (49.5)	8 (36.4)	1.1	1.9	
3	439 (44.8)	14 (63.6)	2.4	3.6	0.14

TABLE 2 continued

Factor	No LRR, n (%)	LRR, n (%)	5-year LRR rate (%)	10-year LRR rate (%)	P value
Adjuvant chemotherapy					
None	590 (59.3)	5 (21.7)	0.5	1	
Received	406 (40.7)	18 (78.3)	3.00	5	0.0004
Adjuvant hormone therapy					
None	366 (36.8)	14 (60.9)	2.3	4.7	
Received	630 (63.2)	9 (39.1)	1.2	1.6	0.01
Any adjuvant therapy					
None	229 (23.1)	5 (21.7)	1.3	2.6	
Received	766 (76.9)	18 (78.3)	1.6	2.7	0.97

^a Largest nodal metastases not recorded in 23 patients

^b Estrogen receptor testing not performed in 74 patients

^c HER2 testing not performed in 363 patients

^d Grade not recorded in 16 patients

Overall, 78.2% of LRRs occurred in women aged ≤ 50 years. Patients aged ≤ 40 years had a 10-year LRR rate of 11.3%, compared with 1.5% for patients aged > 40 ($P < 0.0001$, Table 2, Fig. 1). Of note, patient age ≤ 40 years was the only single variable that was associated with a 10-year LRR rate of $\geq 10\%$ (Table 2). Among the 35 patients ≤ 40 years with node-positive disease, the 5- and 10-year rates of LRR were 9.0 and 12.8%, respectively. The effect of younger age on the risk of LRR was particularly striking among patients without nodal metastases: in patients without metastases, the 5- and 10-year rates of LRR were 0.8 and 1.0%, respectively, in patients > 40 years but 5.3 and 10.5%, respectively, in patients ≤ 40 years ($P < 0.000001$). Among the 60 patients ≤ 40 years with T1N0 disease, the 5- and 10-year LRR

risks were 1.7 and 9.3%, respectively. Among the 18 patients ≤ 40 years with T2N0 disease, the 5- and 10-year LRR rates were both 18.6%. Multivariate Cox regression analysis indicated the only significant independent predictor of LRR was younger age (hazard ratio 2.14; 95% CI, 1.28–3.56; $P = 0.004$).

Relationship Between Nodal Status and Risk of LRR Among Patients with T1 and T2 Disease

In patients with node-positive disease, 5- and 10-year rates of LRR were 2.5 and 3.3%, respectively, among the 176 patients with one positive lymph node and 4.5 and 7.9%, respectively, among the 69 patients with two positive lymph nodes (Table 2; Fig. 2). No LRRs occurred among the 21 patients with three positive lymph nodes. The 10-year risk of LRR was not significantly different between patients without lymph node metastases and patients with one positive lymph node (2.1 and 3.3%, respectively; Table 2; Fig. 2, $P = 0.30$). Patients without lymph node metastases were significantly less likely to have a LRR than patients with two positive lymph nodes (10-year LRR rate, 2.1 vs. 7.9%; Table 2; Fig. 2, $P = 0.003$).

Among the 267 patients with node-positive disease, the presence of lymphovascular invasion was not significantly associated with an increased 10-year risk of LRR (4.9 with vs. 4.1% without invasion). Extranodal extension of ≥ 2 mm was very rare, noted in only 11 patients and only 1 patient with extranodal extension developed LRR. Patients with stage IIB (T2N1) disease had a significantly higher 10-year LRR risk (9.7%) than patients with stage I disease (2%) or stage IIA disease (2.4%) (Table 2; Fig. 2, $P = 0.003$). Among the 189 patients with T1 tumors and 1

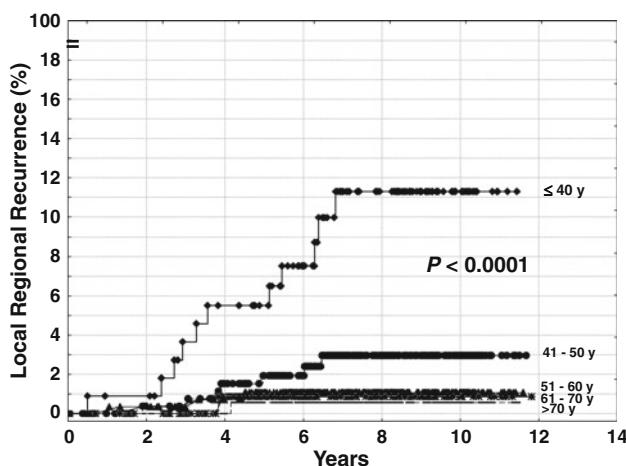


FIG. 1 Risk of locoregional recurrence with respect to age after mastectomy without radiotherapy

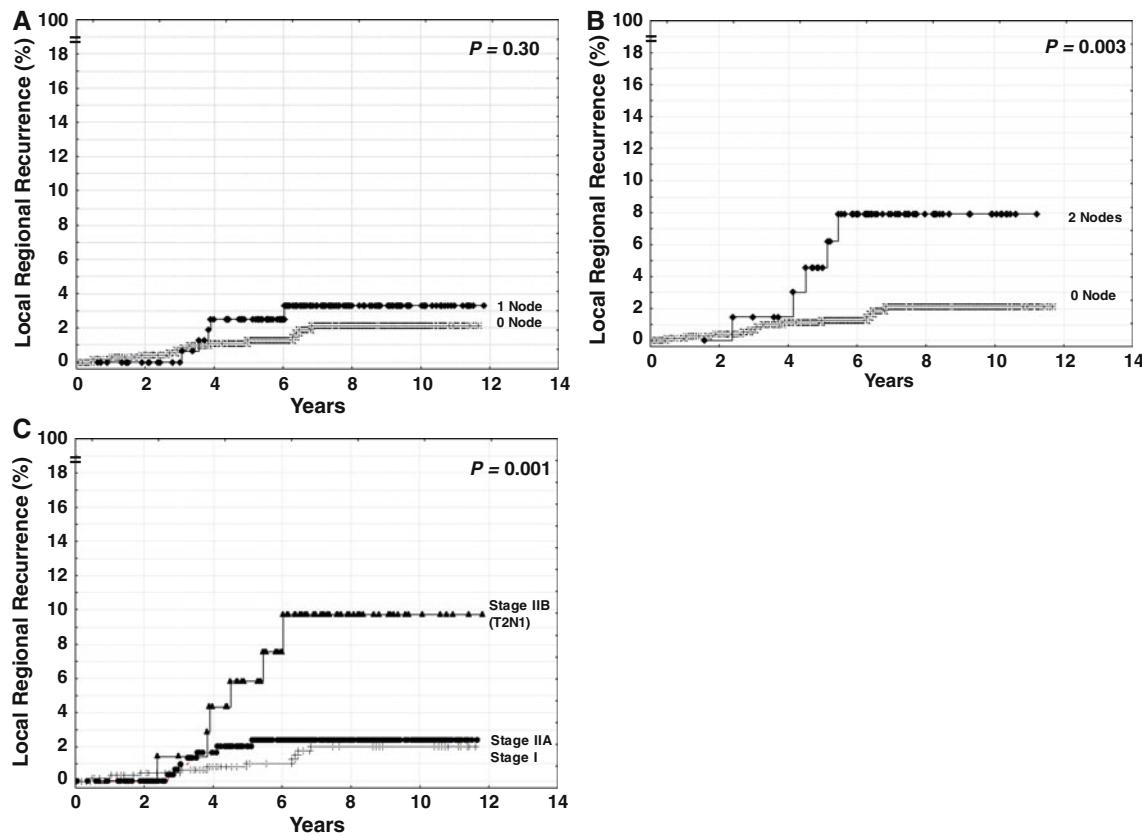


FIG. 2 Risk of locoregional recurrence with respect to nodal status and pathologic stage after mastectomy without radiotherapy. **a** Patients with 0 vs. 1 positive lymph node. **b** Patients with 0 vs. 2 positive lymph nodes. **c** Patients with pathologic stage I vs. IIA or IIIB disease

($n = 131$), 2 ($n = 40$), or 3 ($n = 18$) positive nodes, the 10-year rate of LRR was 2.35%.

Distant Metastasis and DFS

Overall, 51 patients developed an isolated distant metastasis, 12 patients had a distant metastasis and a LRR, and 11 patients had an isolated LRR. The median time to distant metastasis was 3.4 years (95% CI, 3.2–4.4 years). Distant metastatic sites were bone only in 26 patients (41.3%), multiple sites in 23 (36.5%), liver only in 10 (15.9%), lung only in 3 (4.8%), and brain only in 1 (1.6%).

Table 3 lists the 5- and 10-year DFS rates with regard to patient, pathologic, and treatment characteristics. The 5- and 10-year DFS rates for the entire cohort were 94.6 and 91.4%, respectively. On univariate analyses, factors associated with significantly decreased DFS were age ≤ 40 years, T2 tumor, positive lymph nodes, higher stage, estrogen receptor-negative tumor, HER2-positive tumor, higher-grade tumor, and receipt of adjuvant chemotherapy (Table 3). Significant independent predictors of decreased DFS were younger age (hazard ratio 1.68; 95% CI, 1.28–3.56; $P = 0.001$), higher initial presenting stage (hazard

ratio 5.63; 95% CI, 1.55–20.48; $P = 0.009$), and higher grade (hazard ratio 2.79; 95% CI, 1.35–5.80; $P = 0.005$).

Development of Contralateral Breast Cancer

Of the 1019 patients in this cohort, 75 had a synchronous contralateral prophylactic mastectomy, and 50 had bilateral mastectomies for bilateral breast cancer at the time of initial diagnosis. In the remaining 894 patients, 25 contralateral breast cancers (2.8%) developed during follow-up. Of the 25 contralateral breast cancers that developed during follow-up, 18 (72.0%) were invasive and 7 (28.0%) were ductal carcinoma-in-situ. The median time to the development of contralateral breast cancer was 7.22 years (95% CI, 4.9–7.1). The overall 5- and 10-year risks of contralateral breast cancer development—1.0 and 5.5%, respectively—were not significantly different from the competing 5- and 10-year risks of LRR: 1.6 and 2.7%, respectively (Fig. 3; $P = 0.47$). This pattern also held true in the subsets of patients with node-negative disease (5- and 10-year contralateral breast cancer risk, 1.3 and 5.5%, respectively; 5- and 10-year LRR risk, 1.1 and 2.1%, respectively; $P = 0.18$) and node-positive disease (5- and

TABLE 3 Disease-free survival (DFS) rates with regard to patient, pathologic, and treatment-related factors

Factor	5-year DFS rate (%)	10-year DFS rate (%)	P value
Overall	94.6	91.4	—
Age (years)			
≤40	82.1	74.0	
41–50	96.5	92.6	
51–60	96.4	92.9	
61–70	95.9	95.9	
>70	97.7	92.8	<0.0001
Tumor size			
T1	96.1	92.3	
T2	90.1	86.4	<0.0001
No. of positive nodes			
0	96.0	93.2	
1	91.4	84.1	
2	90.9	84.2	
3	94.7	94.7	0.003
Nodal status			
N0	95.6	93.3	
N1	90.2	84.9	0.002
Positive nodes, 0 vs. 1			
0	96.0	93.2	
1	91.4	84.1	0.001
Positive nodes, 0 vs. 2			
0	96.0	93.2	
2	90.9	84.2	0.01
Extranodal extension			
None	95.1	91.5	
<2 mm	89.7	77.5	
≥2 mm	90.0	90.0	0.09
Stage			
I	97.2	94.2	
IIA	91.9	87.3	
IIB (T2, N1)	88.8	81.5	<0.0001
Estrogen receptor status ^a			
Negative	91.7	88.2	
Positive	95.5	91.5	0.03
HER2 status ^b			
Negative	95.8	94.2	
Positive	92.7	81.6	0.03
Lymphovascular invasion			
None	95.4	91.9	
Present	91.4	85.5	0.05
Grade ^c			
1	100	100	
2	96.4	94.1	
3	92.4	87.0	0.001
Adjuvant chemotherapy			
None	97.2	94.0	

TABLE 3 continued

Factor	5-year DFS rate (%)	10-year DFS rate (%)	P value
Received	91.7	87.1	0.0004
Adjuvant hormone therapy			
None	93.4	90.2	
Received	95.7	91.6	0.18
Any adjuvant therapy			
None	95.6	93.6	
Received	94.7	90.4	0.34

^a Estrogen receptor testing not performed in 74 patients^b HER2 testing not performed in 363 patients^c Grade not recorded in 16 patients

10-year contralateral breast cancer risk, 0.4 and 6.5%, respectively; 5- and 10-year LRR risk, 2.9 and 4.3%, respectively; $P = 0.19$.

DISCUSSION

The appropriate use of PMRT for women with T1 and T2 tumors with 0 and 1 to 3 positive lymph nodes has become a subject of immense importance as well as considerable controversy. Because most breast cancer patients in the United States present with early-stage disease, and because few data exist on present-day LRR rates after mastectomy without PMRT, we sought to determine current LRR rates among 1019 patients with these disease characteristics treated at our institution without PMRT during 1997–2002. We found that the overall 10-year risk of LRR for the entire cohort was extremely low: 2.7%.

One finding of significant importance from this analysis was that younger age was the only independent factor associated with the risk of LRR, and only 22% of LRRs occurred in women who were older than 50 years. Several other groups have found younger age to be associated with a significantly higher predicted risk of LRR.^{10,13,18–21} For women ≤40 years without nodal disease, the 10-year risk of LRR was 10.5%. A second major finding from this analysis was that the risk of LRR did not differ significantly between patients without lymph node metastases (10-year risk, 2.1%) and patients with 1 positive lymph node (10-year risk, 3.3%). Because most patients with node-positive disease in the present era will have only 1 positive node, this finding has implications for current national practice guidelines.¹⁴

We are now in a new era of breast cancer detection and treatments. Previous reports of much higher rates of LRR from subset analyses of randomized trials or large data sets for women with 0 to 3 positive nodes were from patients who were diagnosed and treated several decades ago and

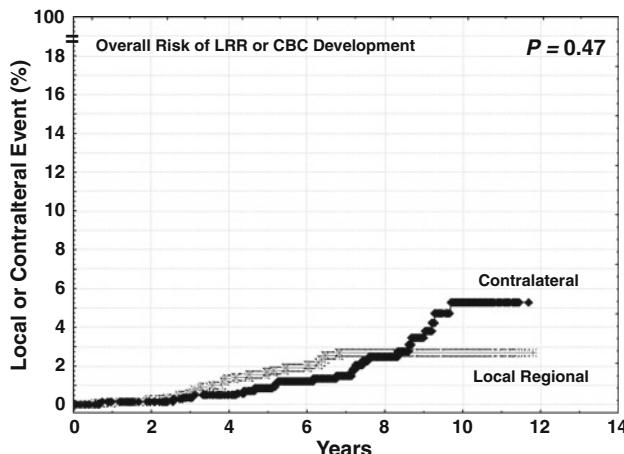


FIG. 3 Risks of contralateral breast cancer development and locoregional recurrence among patients receiving mastectomy without radiotherapy

therefore will not reflect advances in breast cancer management.^{1,2,4,6,8,11–13,18} Many of the previously reported studies included patients treated before the introduction of screening mammography, before the use of standard pathologic margin control, before recognition of the importance of adequate axillary nodal dissection and sentinel node dissection, before the routine use of tamoxifen or aromatase inhibitors for estrogen receptor-positive disease, and before the widespread use of anthracycline- and taxane-based therapies.

Previous studies evaluating the rates of LRR in patients with T1 or T2 disease with 1 to 3 positive lymph nodes have shown the risk to range from approximately 11 to 26%, and several investigators have suggested that PMRT should be considered if such patients have other adverse risk factors for LRR, such as young age, T2 tumor, extranodal extension of >2 mm, inadequate axillary dissection, or lymphovascular space invasion.^{6,8–10,13} Patients with T1 or T2 tumors with 1 to 3 nodal metastases represent a heterogeneous group with respect to clinical and pathologic factors, and reported risks of LRR are dependent not only on the time period studied, but on the patient and tumor characteristics of the patients in the analysis. For example, a previous study from our center on 404 patients with T1 or T2 disease with 1 to 3 positive nodes treated from 1975 to 1994 reported a 10-year total LRR risk of 14%.⁵ However, compared with our present study, that earlier analysis includes a higher proportion of patients with T2 disease (53 vs. 29%) and a higher proportion of patients with largest nodal metastasis of ≥ 1 cm (76 vs. 24%). This may in part explain why we found a much lower overall LRR risk in our current study.⁵

What is the generally accepted level of LRR risk that would justify the use of routine PMRT? Most experts would not recommend routine PMRT if the absolute

overall risk of LRR is <10%, although the precise cutoff point continues to be a subject of debate.^{22,23} In an effort to better define which patients need PMRT, Olivotto and colleagues have shown that a 20% reduction in absolute LRR risk would be expected to confer an improvement in breast cancer-specific survival of approximately 4 to 5%.²² If the LRR risk is <10%, then only 1 to 2 women could potentially obtain a survival benefit for every 100 women receiving PMRT.²² If the absolute theoretical LRR risk is <5%, 200 patients would need to receive PMRT to potentially prevent one to two breast cancer-specific deaths. Despite considerable technical advances in radiation delivery, serious potential short- and long-term complications remain a risk. Therefore, any potential absolute LRR reduction and survival advantage that may be gained from the use of PMRT must be carefully balanced against possible morbidities and future radiation-related mortality.^{2,24–28}

There are several sources of potential bias that need to be considered in interpreting the results of this study. First, we excluded patients who had received neoadjuvant chemotherapy, who may have presented with more advanced disease; therefore, there could be a potential selection bias toward inclusion of patients with an inherently decreased risk for LRR. Second, no conclusions regarding the risk of LRR can be made regarding patients with T1 and T2 tumors and 3 positive lymph nodes because this group represented <2% of patients in this study (the use of PMRT in this subgroup became more common practice at our institution over the course of the study period).⁵ Third, patients not included in the study with 1 to 3 positive nodes with more adverse features could have received radiation during the study period. During this time, at M. D. Anderson Cancer Center, PMRT was more strongly taken into consideration in patients with 1 to 3 positive lymph nodes who had primary tumors >4 cm in size, metastases in 3 positive nodes, positive resection margins, gross extranodal extension, and extensive lymphovascular invasion. Finally, all patients in the present series had negative surgical margins, all reflective of the earlier-stage disease of the entire cohort of patients.

Data from randomized trials concerning the potential risks and benefits of PMRT among women with 1 to 3 positive lymph nodes will not be available for some time. The UK Medical Research Council-sponsored multinational Selective Use of Postoperative Radiotherapy after Mastectomy (SUPREMO) trial (a phase III study) is attempting to address the effect of postmastectomy chest-wall irradiation on overall survival in 3700 patients, including women with pT1 or pT2 tumors and 1 to 3 positive nodes and women with pT2 tumors without positive lymph nodes whose tumors exhibit grade 3 histology or lymphovascular invasion.²⁹

In summary, our findings suggest that overall LRR rates after mastectomy without radiotherapy in patients with T1 and T2 breast cancer are substantially lower in the present era than in studies reported from earlier treatment eras. Patients ≤ 40 years have a relatively high predicted risk of LRR compared with older patients, regardless of nodal status. The extremely low rates of LRR in patients with T1 tumors and 1 or 2 positive nodes do not justify the routine use of PMRT in most patients in this population. The benefits and risks associated with the use of PMRT in patients with T2 tumors with 1 or 2 positive nodes should be carefully discussed with patients. Recently, there has been work toward the use of biologic and genetic multi-parameter assays to help predict LRR.^{30,31} In the absence of other large cohort studies or present-era randomized data, we hope that other factors will be pursued, not only to refine estimates of LRR, but also to predict sensitivity to radiotherapy.

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